NTP Workshop: Hormonally-Induced Reproductive Tumors – Relevance of Rodent Bioassays.

The findings of the workshop have been submitted to *Environmental Health Perspectives* for publication. Current status: Accepted for publication after revision.

Major Workshop recommendations

- Utilize alternative models (i.e., genetically engineered, *in vitro*, etc.) to develop sensitive models for detecting specific types of tumors

NTP perspective: Identifying appropriate alternative models is especially important for prostate and ovarian cancers because the conventional rodent models are not (very) predictive for these tumor types. The NTP has utilized the Transgenic Adenocarcinoma of the Mouse Prostate (TRAMP) model to address the impact of dietary antioxidants and dietary restriction on prostate cancer development. However, current studies generally focus on the ability of substances to inhibit prostate cancer development and the NTP needs to perhaps place a greater emphasis on exploring the use of the TRAMP and other models to identify substances that enhance prostate carcinogenesis.

- Include additional endocrine responsive endpoints

NTP perspective: All of the breakout groups had suggestions for pre-neoplastic responses or molecular markers that could potentially be included in prechronic studies. With respect to hormone-mediated tumors, the NTP is most interested in markers that are predictive for tumorigenesis and relevant to human disease. Suggested endocrine responsive assays and endpoints include *in vitro* assays to assess estrogen or androgen receptor binding, some of the short-term screens being evaluated by the Environmental Protection Agency as part of its Endocrine Disruptor Screening Program, and whole mounts of mammary glands. In addition, the mammary and prostate breakout groups both identified IGF-1 as an important stimulant and potentially useful marker of tumorigenic response. In the long-term, the NTP would like to include *in vitro* assays that screen for potential endocrine activity in its High Throughput Screening Initiative (see *http://ntp.niehs.nih.gov/go/28213* for more information on this initiative). In the short-term, the NTP foresees more routine assessment of *in vivo* endocrine endpoints, such as whole mounts of mammary glands, when preliminary data suggest an endocrine mode of action or effect.

- Discontinue use of the F344/N rat

NTP perspective: The NTP has moved to the utilization of the *Wistar Han* rat for standard carcinogenicity and other rat toxicity studies (e.g reproduction and development). Utilizing the same strain for all NTP studies would minimize the need to

conduct multiple preliminary and toxicokinetic studies and enhance comparability across study endpoints.
[see also response on stocks and strains workshop].

- Evaluate the importance of developmental programming in hormonally dependent tissues leading to pre-neoplastic events and tumors

NTP perspective: NTP has long recognized the scientific appeal of including an *in utero* or perinatal exposure component in its chronic bioassays. The NTP recently decided to incorporate perinatal exposure in its chronic carcinogenicity studies as the default study design for rats. This means that future substances slated for carcinogenicity studies will include early in-life exposure *unless* there is a compelling reason to do otherwise (e.g., insufficient exposure to pregnant women and children, lack of placental transfer or accumulation in the fetus, etc.). In exceptional cases, the NTP may need to conduct multiple bioassays for each compound to address the carcinogenic potency for various periods of exposure (i.e., *in utero* only, *in utero* + adult, and adult only). However, the cost of conducting these types of comparative studies is prohibitive for routine practice. NTP scientists are also considering other approaches to address early in-life exposures including maintaining the F_1 animals generated in reproductive studies for chronic studies and/or strategies to evaluate perinatal exposures in subchronic studies.